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Review Article

Personality disorders

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CONTENTS

Abstract

The classification of personality disorders according to DSM-IV-TR is based on 10 specific disorders that are grouped into 3 clusters based on their descriptive similarities. However, individuals frequently present with co-existing personality disorders from different clusters and other psychiatric disorders, including depression. These co-morbidities make the conduct of clinical studies very challenging, particularly in the selection of adequate and evaluable patient populations. The only personality disorder which has been widely studied in the context of pharmacological intervention is borderline personality disorder (BPD). Drugs from the following classes –antidepressants, atypical antipsychotics and antiepileptics– have been evaluated in the treatment of BPD. A number of randomized, controlled studies have been conducted. These have generally been small studies, with the exception of two large multicenter studies with the atypical antipsychotic olanzapine. There is evidence to support the use of drugs within all these classes, although many different rating scales have been used in the clinical studies, making interpretation difficult. It is likely that an individual patient's treatment is most often based on physician preference rather than evidence from controlled studies.

Introduction

According to DSM-IV-TR (1), a personality disorder is defined as an enduring pattern of inner experience and behavior that deviates markedly from the expectations of the individual's culture. It is pervasive and inflexible, has an onset in adolescence or early adulthood, is stable over time, and leads to distress or impairment. There are 10 specific personality disorders that are grouped into 3 clusters based on their descriptive similarities. These are described as follows:

- Cluster A (individuals often appear odd or eccentric)
  - Paranoid personality disorder
  - Schizoid personality disorder
  - Schizotypal personality disorder
- Cluster B (individuals often appear dramatic, emotional or erratic)
  - Antisocial personality disorder
  - Borderline personality disorder
  - Histrionic personality disorder
  - Narcissistic personality disorder
- Cluster C (individuals often appear anxious or fearful)
  - Avoidant personality disorder
  - Dependent personality disorder
  - Obsessive-compulsive personality disorder

Although the clustering system is relevant in some research and educational situations, it has not been consistently validated. Individuals frequently present with co-existing personality disorders from different clusters. In addition, an individual may not meet the criteria for any specific personality disorder, or may have a disorder that is not included in the classification. These cases are categorized as Personality Disorder Not Otherwise Specified (NOS).

The pattern of inner experience and behavior that defines the personality disorder is manifested in at least two of the areas of cognition, affectivity, interpersonal functioning or impulse control. This feature of a personality disorder represents criterion A for the general diagnosis of the disorder. Evaluation and diagnosis require an assessment of an individual's long-term patterns of functioning, and personality traits must be distinguished from characteristics that emerge in response to specific situational stressors. Personality traits are diagnosed as a personality disorder only when they are inflexible, maladaptive and persistent, and cause significant functional impairment or subjective distress. Diagnosis is also frequently complicated by the fact that the individual may not consider the characteristics that define the personality disorder to be problematic.

Pharmacological intervention in the treatment of personality disorders is confounded by the high incidence of co-existing morbidities, particularly other psychiatric dis-

orders, including depression. By far the largest body of recent and ongoing clinical studies in the evaluation of pharmacological intervention in personality disorders relates to borderline personality disorder within Cluster B. A review of the current status and outcome of studies in patients with this disorder will be the main focus of this article, together with a brief summary of findings in schizotypal personality disorder.

Borderline personality disorder

Borderline personality disorder (BPD) is both a serious and frequent psychiatric disorder. It is characterized by an early onset and pervasive pattern of instability in interpersonal relationships, self-image and affect regulation, and marked impulsivity is present in a variety of contexts (1-3). The prevalence of BPD is estimated to be about 1-2% of the general population and about 10% among individuals in outpatient mental health clinics. BPD frequently co-occurs with other personality disorders and has an estimated prevalence of 30-60% among clinical populations with personality disorders (1). In addition, patients with BPD often meet criteria for other psychiatric disorders, including affective and anxiety disorders, eating disorders, substance-related disorders and attention deficit hyperactivity disorder (ADHD) (1, 3). There are nine diagnostic criteria for BPD in DSM-IV-TR and a patient must meet five of these for diagnosis (1). It is therefore possible for two people to meet the criteria for diagnosis and yet have very different personalities. As a result of the heterogeneities of patients with BPD, care and treatment are likely to originate from a diverse source of providers, including psychiatric facilities, casualty departments and primary care physicians. The heterogeneity also presents a challenge in assessing the impact of intervention in BPD. Although psychotherapy is the mainstay of treatment for BPD, pharmacotherapy, often involving polypharmacy regimens, is frequently prescribed (4). Clinical studies of experimental drug therapies for BPD are summarized in Tables I and II.

A review of pharmacological interventions for people with BPD was conducted in October 2002 using a systematic search of 26 specialist and bibliographic databases (5). All relevant randomized, controlled trials with or without blinding were considered for the review. Ten relevant studies were identified of between 1 and 6 months' duration and involving a total of 554 subjects. The largest study included 108 subjects. Interventions included treatment with antidepressants, antipsychotics and mood stabilizers. The authors concluded that overall there was poor reporting of methods, resulting in potentially biased results. The principal conclusion was that pharmacological treatment of subjects with BPD was not based on good evidence from trials, and that the positive effect of antidepressants could be considerable. The authors recommended trials of adequate power and duration comparing a safe antidepressant with placebo for clinically meaningful outcomes.

Researchers in Italy conducted a meta-analysis of published randomized, placebo-controlled trials to determine whether pharmacotherapy was effective against the fixed and stable core traits of BPD (6). Comprehensive searches of the Medline, Embase, PsychLit and Cochrane Central Register of Controlled Trials databases were performed for records up to June 2006. Twenty-two placebo-controlled comparisons were included in the meta-analysis; 8 studies involved antipsychotics, 7 antidepressants and 7 mood stabilizers. The authors concluded that pharmacotherapy can exert a modest beneficial effect on some core traits of BPD; notably, antidepressants and mood stabilizers were effective against instability and anger, while antipsychotics as a class had a positive effect with regard to impulsivity and aggression, interpersonal relationships and global functioning. Drugs particularly identified within these classes were fluoxetine, topiramate and lamotrigine.

Antidepressants in BPD

Despite the recommendations in the Cochrane Systematic Review (5), very few recent studies of antidepressants have been performed. A small number of studies have been conducted with 5-HT reuptake inhibitors. These have included a double-blind, placebo-controlled, randomized trial of the selective serotonin reuptake inhibitor (SSRI) fluvoxamine in 38 nonschizophrenic, nonbipolar female patients with BPD. In this study, fluvoxamine demonstrated a statistically significant and clinically relevant effect on the occurrence of rapid mood shifts, but no effect on impulsive and aggressive behavior (7). With regard to fluoxetine, the only recently conducted study was a randomized, double-blind, placebo-controlled study of fluoxetine added to dialectical behavior therapy (DBT). Fluoxetine did not demonstrate an advantage over placebo for any outcome measure (8). A randomized, double-blind, placebo-controlled trial of escitalopram in patients receiving 6 months of DBT is ongoing (9).

Based on the overall body of evidence supporting the use of SSRIs in BPD, they are widely used in treating BPD, particularly in patients with the target symptoms of depression and impulsivity. SSRIs are the first-line pharmacological treatment for affect dysregulation and impulse behavioral symptoms of BPD, as defined in the American Psychiatric Association's Practice Guideline for the Treatment of Patients with BPD (10).

Atypical antipsychotics – olanzapine and quetiapine

The majority of the more recent literature regarding pharmacotherapy of BPD reports on studies with the 5-HT_2 and dopamine D2 antagonists olanzapine and quetiapine. These are atypical antipsychotics marketed for the treatment of schizophrenia and also for manic episodes associated with bipolar disorder. A double-blind, placebo-controlled pilot study of olanzapine was conducted in 28 female subjects with BPD. Olanzapine was associated with a significantly greater rate of improvement

Table I: Clinical studies assessing the use of antidepressants and antipsychotics for borderline personality disorder (BPD) (from Prous Science Integrity®).

Drug	Design	Treatments	n	Conclusions	Ref.
Fluvoxamine	Randomized Double-blind Crossover	Fluvoxamine, 150 mg/d p.o. x 6 wks Placebo	38	Fluvoxamine significantly improved rapid mood shifts in women with BPD, but did not improve impulsivity or aggressiveness	7
Fluoxetine	Randomized Double-blind	Fluoxetine, 40 mg/d [titrated from 20 mg/d over 3 wks] p.o. + Dialectical behavior therapy Placebo + Dialectical behavior therapy	25	Fluoxetine added to psychosocial therapy did not provide additional benefits to patients with BPD	8
Escitalopram	Randomized Double-blind	Escitalopram + Dialectal behavior therapy x 6 mo Placebo + Dialectal behavior therapy x 6 mo	NA	A study was initiated to evaluate the effect of escitalopram in combination with dialectal behavior therapy for the treatment of BPD	9
Olanzapine	Randomized Double-blind	Olanzapine [titrated from 1.25 mg/d] p.o. x 6 mo Placebo	28	Olanzapine was safe and effective for the treatment of women with BPD	11
	Randomized Double-blind	Olanzapine, 2.5-20 mg/d [titrated from 2.5 mg/d] p.o. x 12 wks Placebo	40	Olanzapine was effective for the symptomatic treatment of BPD	12
	Comparative Randomized Double-blind	Olanzapine [titrated from 2.5 mg/d] p.o. x 8 wks Fluoxetine [titrated from 10 mg/d] p.o. x 8 wks Olanzapine [titrated from 2.5 mg/d] + Fluoxetine [titrated from 10 mg/d] p.o. x 8 wks	45	Fluoxetine, olanzapine or the combination of both were all safe and effective for the treatment of women with BPD. All treatments significantly improved chronic dysphoria and impulsive aggression, but olanzapine, both as monotherapy and in combination with fluoxetine, was more effective than fluoxetine for the treatment of these two symptoms	13
	Randomized Double-blind	Olanzapine, 5-20 mg/d p.o. + Dialectal behavior therapy x 12 wks Placebo + Dialectal behavior therapy x 12 wks	60	Olanzapine in combination with psychotherapy was effective for the treatment of BPD	14
	Multicenter Randomized Double-blind Dose-finding	Olanzapine, 2.5-20 mg/d p.o. x 12 wks Placebo	314	Olanzapine and placebo were associated with clinically but not statistically significant improvements in BPD symptoms	15
	Multicenter Randomized Double-blind Dose-finding	Olanzapine, 2.5 mg/d p.o. x 12 wks Olanzapine, 5-10 mg/d p.o. x 12 wks Placebo	451	Olanzapine at moderate doses (5-10 mg/day) was effective for the treatment of overall borderline psychopathology, with statistically significant differences compared to placebo in improvements in the Zanarini Rating Scale for BPD	16
	Open Comparative	Olanzapine, 10 mg i.m. Ziprasidone, 20 mg i.m.	20	Olanzapine and ziprasidone were effective, rapid-acting and safe for treating patients with acute BPD	17
	Open	Olanzapine, 10 mg i.m.	25	Intramuscular olanzapine monotherapy was well tolerated and significantly reduced agitation in patients with BPD	18
	Open	Olanzapine x 8 wks	15	This study will evaluate the effects of olanzapine on brain positron emission tomography (PET) parameters in patients with BPD	19
Quetiapine	Open	Quetiapine, 400 [max.] mg/d [titrated from 50 mg/d] x 12 wks	34	Low-dose quetiapine showed a strong positive clinical impact, including impulsivity, in patients with severe BPD with limited psychotic symptoms	20

Continuation

Table I (Cont.): Clinical studies assessing the use of antidepressants and antipsychotics for borderline personality disorder (BPD) (from Prous Science Integrity®).

Drug	Design	Treatments	n	Conclusions	Ref.
Quetiapine	Open	Quetiapine, 200-400 mg/d [titrated from 25 mg/d] p.o. x 12 wks	14	Quetiapine was well tolerated and effective for the treatment of BPD, especially in the presence of prominent symptoms related to impulsiveness and/or aggressiveness	21
	Open	Quetiapine, 150-400 mg p.o. b.i.d. [titrated from 50 mg b.i.d. over 3 d] x 12 wks	29	Quetiapine was effective for the treatment of certain features of BPD, including low mood and aggression	22
	Multicenter Retrospective	Quetiapine, 422 [mean] mg/d p.o.	105	Quetiapine treatment was effective in most patients with BPD	23
	Multicenter Randomized Double-blind	Quetiapine, 200-600 mg/d x 8 wks Placebo	40	This clinical trial will provide data on the efficacy of quetiapine in treating psychotic-like symptoms in patients with BPD	24
	Open	Quetiapine	15	This study will determine the efficacy, safety and tolerability of quetiapine in patients with BPD	25
Risperidone	Open	Risperidone, 4 [max] mg [titrated from 1 mg/d] x 8 wks	15	Low to moderate doses of risperidone improved symptoms of BPD	26
Aripiprazole	Randomized Double-blind	Aripiprazole, 15 mg/d p.o. x 20 mo Placebo x 8 wks → Aripiprazole, 15 mg/d p.o. x 18 mo	52	Aripiprazole was safe and effective, and produced significant changes in all assessment scales in treated patients with BPD	27, 28

NA: not available

over time compared with placebo in all four core areas of affect, cognition, impulsivity and interpersonal relationships (11). In 40 BPD patients, the results of a double-blind, placebo-controlled study showed olanzapine was significantly superior to placebo based on the primary outcome measure of the Clinical Global Impressions scale modified for BPD (CGI-BPD) (12). In a preliminary, randomized trial of fluoxetine, olanzapine and their combination in 45 female patients with BPD, olanzapine monotherapy and the combination were more effective than fluoxetine monotherapy in treating the dimensions of chronic dysphoria and impulsive aggression of BPD (13). Sixty patients with BPD were also included in a double-blind, placebo-controlled study of DBT plus olanzapine. Olanzapine was associated with a statistically significant improvement compared with placebo in depression, anxiety and impulsivity/aggressive behavior (14).

Two much larger double-blind, placebo-controlled studies with olanzapine have recently been reported. These were industry-sponsored, phase III studies in patients meeting all of the DSM-IV-TR general diagnostic criteria for a personality disorder and meeting the DSM-IV-TR diagnostic criteria for BPD. The primary efficacy measure in both studies was the improvement in overall symptomatology in the Zanarini Rating Scale for BPD (ZAN-BPD) total score over the 12-week period of study. In the first study of flexibly dosed olanzapine (2.5-20 mg/day; n=155) *versus* placebo (n=159), both treatment groups showed significant improvements in overall symptom severity, but did not differ in the magnitude of improvement at endpoint. Response rates (at least a 50% reduction in ZAN-BPD total score) did not differ between treatment groups; however, time to response was significantly shorter for the olanzapine treatment group. Olanzapine treatment was also associated with an increased incidence of somnolence, sedation and weight gain; the latter was significantly greater in olanzapine-treated patients (15).

In the second study comparing low (2.5 mg/day; n=150) and moderate (5-10 mg/day; n=148) doses of olanzapine with placebo (n=153), moderate doses were associated with statistically significant differences compared with placebo in the primary endpoint (changes in the ZAN-BPD total score of –8.50 and –6.79, respectively; $p = 0.010$). Response rates and time to response were also significantly improved in the moderate-dose group compared with placebo. The adverse event profile in this study was similar to that observed in the flexible-dosing study. The second study demonstrated that moderate doses of olanzapine are effective in the treatment of overall borderline psychopathology (16).

Two recent nonrandomized studies have also demonstrated that intramuscular olanzapine (10 mg) may be effective in the treatment of acute agitation in BPD patients presenting to emergency departments (17, 18). An ongoing study is comparing baseline and endpoint

positron emission tomography (PET) scans in 15 patients treated with olanzapine. The objective of this study is to observe brain correlates of olanzapine treatment response and to compare the baseline scans with those of normal controls (19).

There have been no randomized, double-blind, placebo-controlled studies reported with quetiapine. However, a number of open-label studies of 12 weeks' duration have indicated that quetiapine may also be effective in the treatment of various features of BPD, including low mood and aggression (20-22). A recently reported study, the TREBOL study, was a multicenter, retrospective study of 105 BPD patients treated with quetiapine for the previous 6 months. The CGI-Change showed that almost 95% of patients improved in the 6 months of treatment, and with regard to patients' attitude and compliance, most of the patients perceived quetiapine treatment positively and showed high levels of compliance (23). A randomized, double-blind, placebo-controlled study of the effect of quetiapine on psychotic-like symptoms and the severity of psychiatric symptoms is ongoing and has an expected enrollment of 40 patients with BPD (24). A 6-week, open-label, flexible-dosing study of quetiapine in 15 patients with BPD is also under way (25).

Atypical antipsychotics – risperidone and aripiprazole

An 8-week, open-label study of risperidone in 15 patients with BPD indicated that it may be effective in reducing aggression and depressive symptoms, and also in increasing energy and global functioning (26). However, no randomized, placebo-controlled studies with risperidone have been performed.

A randomized, double-blind, placebo-controlled study of aripiprazole was conducted in 52 patients with BPD. The rates of improvement over the course of the 8-week study were significantly greater in patients treated with aripiprazole compared with placebo for the primary outcome parameters: the Symptom Checklist (SCL-90-R) scale, with the exception of somatization, the Hamilton Rating Scales (Depression and Anxiety) and the State-Trait Anger Expression Inventory (STAXI). No significant change in weight was observed (27). In an 18-month follow-up of these patients, with observations carried out every 6 months, the significant improvements in the aripiprazole group were maintained, indicating that it may be a safe and effective drug for improving borderline symptomatology (28).

Antiepileptics – topiramate, lamotrigine, oxcarbazepine and divalproex sodium

The sodium channel blockers topiramate, lamotrigine and oxcarbazepine were launched in the 1990s for the treatment of epilepsy, and in recent years their efficacy in the treatment of BPD has been evaluated.

Two randomized, double-blind, placebo-controlled studies of topiramate in female patients with BPD have been performed. In the first study, 31 subjects were assigned to topiramate in a 2:1 ratio, and statistically significant improvements compared with placebo were observed in the primary outcome measures: self-reported changes on 4 of the 5 anger subscales of the STAXI after 8 weeks of treatment (29). A subsequent study by the same group of researchers determined whether topiramate could influence patients' borderline psychopathology, health-related quality of life and interpersonal problems. In this study, 56 female patients were assigned to treatment in a 1:1 ratio for 10 weeks. Statistically significant changes were observed in 6 of 10 scales of the SCL-90-R, all 8 scales of the SF-36 Health Survey and 4 of 8 scales of the Inventory of Interpersonal Problems (30). In both studies, significantly greater weight loss was observed in topiramate-treated patients. A randomized, double-blind, single-center study with an anticipated enrollment of 30 patients was initiated in March 2007 to evaluate the efficacy of topiramate in patients with BPD and alcohol dependence (31).

The efficacy of lamotrigine in the treatment of aggression in 27 female BPD patients was evaluated in a randomized, double-blind, placebo-controlled study. Statistically significant changes on four subscales of the STAXI were observed after 8 weeks of treatment (32). A retrospective study in 13 female BPD patients also showed that lamotrigine was able to reduce affective instability in these patients (33).

An open-label, 12-week pilot study in 17 patients with BPD indicated that oxcarbazepine may also be effective in the management of BPD, as demonstrated by statistically significant improvements in CGI-Severity of Illness, Brief Psychiatric Rating Scale (BPRS) mean score and BPD Severity Index total score (34).

Divalproex sodium is a GABAergic transmission enhancer that was launched in 1983 for the treatment of epilepsy. It is also approved for the treatment of manic episodes associated with bipolar disorder. A preliminary double-blind, placebo-controlled trial in 16 patients with BPD indicated that divalproex sodium may be effective in treating the global symptomatology of BPD, although the differences between the groups were not statistically significant (35). A recent open-label study in 20 patients showed that extended-release divalproex sodium was associated with statistically significant improvements in the CGI-Improvement scale and the Global Assessment Scale, the primary outcome measures. There were also statistically significant improvements in aggressive behavior, as measured by the Overt Aggression Scale-Modified (OAS-M) irritability subscale and the Aggression Questionnaire, but not on measures of affective disturbance, dissociation or general psychopathology (36). The efficacy of divalproex sodium in the treatment of impulsive aggression was also evaluated in patients with a Cluster B personality disorder (n=96), intermittent explosive disorder (n=116) or post-traumatic stress disorder (n=34). This was a 12-week, randomized, double-blind, placebo-controlled study. In the subgroup of patients with Cluster B personality disorders, a statistically significant difference in favor of divalproex sodium was observed for OAS-M Aggression and Irritability scores over the last 4

Table II: Clinical studies assessing the use of antiepileptics and other drug therapies for borderline personality disorder (BPD) (from Prous Science Integrity®).

Drug	Design	Treatments	n	Conclusions	Ref.
Topiramate	Randomized Double-blind	Topiramate, 250 mg/d [titrated from 50 mg/d over 6 wks] p.o. x 8 wks Placebo	31	Topiramate was safe and effective for the treatment of anger in women with BPD	29
	Randomized Double-blind	Topiramate, 200 mg/d [titrated from 50 mg/d over 6 wks] p.o. x 10 wks Placebo	56	Topiramate was safe and effective for the treatment of women with BPD	30
	Randomized Double-blind	Topiramate, 250 mg/d p.o. Placebo	30	This study will evaluate the efficacy of topiramate in decreasing aggression and reducing alcohol consumption in patients with co-morbid BPD and alcohol dependence	31
Lamotrigine	Randomized Double-blind	Lamotrigine, 50 mg/d p.o. x 2 wks → 100 mg/d p.o. x 1 wk → 150 mg/d p.o. x 2 wks → 200 mg/d p.o. x 3 wks Placebo	27	Lamotrigine was safe and effective for controlling anger in women with BPD. Lamotrigine was not associated with any clinically significant effect on body weight	32
	Retrospective	Lamotrigine, 50-200 mg/d x 3 [min.] mo	13	Lamotrigine was safe and effectively reduced symptoms of affective instability in female patients with BPD	33
Oxcarbazepine	Open	Oxcarbazepine, 1200-1500 mg/d [titrated from 600 mg/d over 4-5 d] p.o. x 12 wks	17	Oxcarbazepine treatment was effective on a broad spectrum of BPD symptoms: affective instability, impulsivity, outbursts of anger and interpersonal relationships	34
Divalproex sodium	Randomized Double-blind	Valproate [titrated from 250 mg/d to C_{ss} 80 µg/ml or highest tolerated dose] p.o. x 10 wks Placebo	16	Valproate was well tolerated but not more effective than placebo in improving global symptomatology, level of functioning, aggression and depression in patients with BPD	35
	Open	Valproate ER [titrated from 250 mg/d over 6 wks up to highest tolerated dose within therapeutic range] p.o. x 12 wks	20	Treatment with valproate extended-release formulation improved global symptoms, irritability and aggression in patients with BPD	36
Naltrexone	Open	Naltrexone, 25-100 mg/d p.o. q.i.d. x 2 [min] wks	13	Naltrexone improved dissociative symptoms, including flashbacks, in women with BPD	38
	Multicenter Randomized Double-blind Crossover	Naltrexone, p.o. Placebo	48	This clinical study will investigate if naltrexone is able to reduce the intensity and duration of flashbacks and dissociative states in patients with BPD	40
Naloxone	Randomized Double-blind Crossover	Naloxone, 0.4 mg i.v. Placebo	9	A single intravenous dose of naloxone 0.4 mg was not superior to placebo for the treatment of acute dissociative disorders in women with BPD	39
Guanfacine	Randomized Double-blind	Guanfacine x 8 wks Placebo	NA	A study was initiated to evaluate the efficacy of guanfacine for the treatment of BPD	41
Clonidine	Randomized Single-blind	Clonidine, 75 µg p.o. [first acute state] → 150 µg p.o. [second acute state] Clonidine, 150 µg p.o. [first acute state] → 75 µg p.o. [second acute state]	14	Oral clonidine was effective for the treatment of acute states of aversive inner tension, dissociative symptoms and impulsive self-injurious behavior in women with BPD	42

NA: not available

weeks of treatment, and for CGI-Severity at multiple time points throughout the study. Across psychiatric diagnoses, more patients in the divalproex sodium group discontinued because of an adverse event (17% *versus* 3% in the placebo group; $p < 0.001$) (37).

Others

The opioid receptor antagonists naltrexone and naloxone have been investigated in the treatment of dissociative symptoms in patients with BPD. A small open-label

study of oral naltrexone indicated that these symptoms may respond to treatment with opioid receptor antagonists (38); however, this was not supported by a double-blind, placebo-controlled, crossover study with intravenous naloxone (39). A randomized, double-blind, placebo-controlled, crossover study to evaluate the efficacy of naltrexone on the incidence and intensity of flashbacks and dissociative states in BPD patients is ongoing. The study has an anticipated enrollment of 48 patients (40). The α_2-adrenoceptor agonist guanfacine, an antihypertensive agent, is also being investigated for the treatment of BPD (41); clonidine previously showed some evidence of efficacy in a randomized, single-blind study in BPD patients with acute aversive inner tension and self-injurious behavior (42).

Schizotypal personality disorder

Very few studies have been reported for the treatment of schizotypal personality disorder. A small double-blind, placebo-controlled study indicated that physostigmine, an anticholinesterase inhibitor, may improve visuospatial working memory (43), and a small open-label study with olanzapine demonstrated significant improvements in psychosis, depression ratings and overall functioning (44). A randomized, double-blind, placebo-controlled study of low-dose risperidone was conducted in 25 patients with schizotypal personality disorder. Patients treated with risperidone had statistically significantly lower scores on the Positive and Negative Syndrome Scale (PNSS) total, negative, general and positive symptom scales during 9 weeks of treatment compared to those receiving placebo (45). Most recently, guanfacine has been shown to improve context-processing abnormalities in schizotypal personality disorder (46), and a randomized, double-blind, crossover study is ongoing to determine the efficacy of guanfacine in improving cognitive symptoms. The anticipated enrollment in this study is 80 patients (47). Information on these treatment approaches is summarized in Table III.

Other personality disorders

There are no recent studies reported in other personality disorders, other than case studies or case series (48-50), or small studies in mixed personality disorders or personality disorders with co-morbidities such as depression, schizophrenia, bipolar disorder or opioid dependence (51-56). These were not considered in the context of this review.

Conclusions

Very few randomized, controlled studies have been conducted in the treatment of personality disorders, with the exception of BPD. This is most likely due to the mixed etiology of personality disorders and the multiple co-morbidities with which patients present. The definition of patient populations for studies thus becomes a challenge and objective outcomes cannot be determined. Despite the Cochrane Systematic Review and subsequent meta-analysis of studies in BPD, controlled, randomized studies in this disorder are still sparse, thus providing poor evidence for the efficacy of pharmacotherapy in BPD. Despite the recommendation of the American Psychiatric Association for SSRIs as first-line pharmacological treatment for affect dysregulation and impulse behavioral symptoms of BPD, recent studies have focused on the class of atypical antipsychotics and have demonstrated their potential efficacy in this disorder. The largest studies

Table III: Clinical studies of experimental therapies for schizotypal personality disorder (from Prous Science Integrity®).

Drug	Design	Treatments	n	Conclusions	Ref.
Physostigmine	Randomized Double-blind Crossover	Physostigmine, 0.014 mg/kg i.v. infusion over 20 min Physostigmine, 0.014 mg/kg i.v. infusion over 60 min Placebo	10	Physostigmine improved visuospatial working memory, but not serial verbal learning performance, in patients with schizotypal personality disorder	43
Olanzapine	Open	Olanzapine, 2.5-12.5 mg/d [titrated from 2.5-5 mg/d] p.o.x 26 wks	11	Olanzapine was well tolerated and effective for the treatment of schizotypal personality disorder	44
Risperidone	Multicenter Randomized Double-blind	Risperidone, 0.25 mg/d p.o. x 1 wk → 0.5 mg/d p.o. x 2 wks → 1 mg/d p.o. x 2 wks → 1.5 mg/d p.o. x 2 wks → 2 mg/d p.o. x 2 wks Placebo	25	Low-dose risperidone was generally well tolerated and effectively reduced symptom severity in patients with schizotypal personality disorder	45
Guanfacine	Randomized Double-blind	Guanfacine, 2 mg/d p.o. [titrated over 2 wks] x 4 wks Placebo	29	After treatment with guanfacine, subjects with schizotypal personality disorder showed an improvement of context processing, making fewer BX errors (false clue, correct probe) and more AY errors (correct clue, false probe)	46
	Randomized Double-blind Crossover	Guanfacine, 2 [max.] mg/d x 8 wks Placebo	80	This study will evaluate the efficacy of guanfacine as a symptomatic treatment of schizotypal personality disorder	47

ever conducted in BPD support the use of moderate doses of olanzapine in overall borderline psychopathology. There has also been recent interest in the evaluation of the antiepileptics –topiramate, lamotrigine, oxcarbazepine and divalproex sodium– and there is some evidence to support their use, particularly in the treatment of anger and aggression associated with BPD.

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